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REVIEW PAPER

Paediatric oncology and haematology in Poland: position paper

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ABSTRACT

Paediatric oncology is a discipline of rare diseases, defined by incidence lower than five cases per 10,000 people. Around 1160 new cases of childhood malignancies are diagnosed every year in Poland (2016–2017). The incidence rate is about 151 children per 1 million paediatric population a year. It is calculated that one out of 6600 children develops malignancy during one calendar year. Children with oncological diseases are treated in

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18 centres accredited by the Polish Society of Paediatric Oncology and Haematology. Modern treatment for childhood cancer is based on multimodal therapy including multi-agent chemotherapy, radiotherapy, surgery, haematopoietic cell transplantation, and immunotherapy. All children in Poland are treated according to international therapeutic protocols in cooperation with international centres, which run as academic clinical trials. With this approach children with malignancy in Poland receive the same treatment as children in Western Europe. In this review we present current advances in diagnostics, treatment, and supportive care in paediatric oncology and haematology in Poland.

KEY WORDS:

paediatric oncology, paediatric haematology, children, epidemiology, outcome.

INTRODUCTION

Paediatric oncology is a discipline of rare diseases, defined by incidence lower than five cases per 10,000 people. Each paediatric malignancy fulfils this criterion.

Around 1160 new cases of childhood malignancies are diagnosed every year in Poland (2016–2017). The incidence rate is about 151 children per 1 million paediatric population a year (in 2017 the population of children under 18 years old constituted 7.65 million in Poland). It is calculated that 1 out of 6600 children develops malignancy during one calendar year. The distribution of paediatric malignancies in Poland in 2016–2017 is shown on Figure 1 and it remains stable over the years [1].

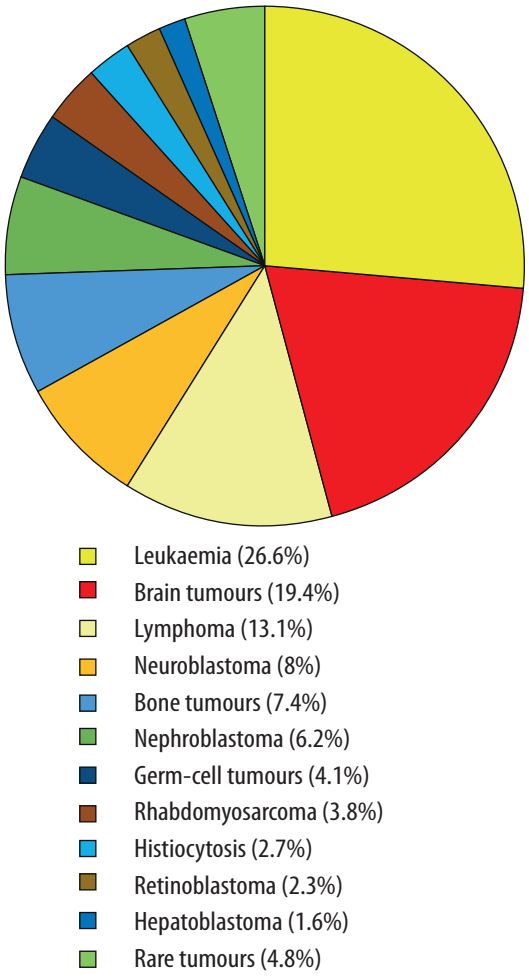

FIGURE 1. The distribution of malignancy in children in Poland in 2016–2017

With over 163,000 newly diagnosed cancer cases reported in Poland in 2015, paediatric malignancies accounted for about 0.71%.

SYSTEM OF MEDICAL CARE

Children with oncological diseases are treated in 18 centres accredited by the Polish Society of Paediatric Oncology and Haematology (Fig. 2). The system of medical care in paediatric oncology and haematology in Poland is based on regional (provincial) centres: one centre per province in 12 cases; three centres in two provinces with the largest numbers of inhabitants (Warsaw and Upper Silesia); while two regions with the lowest number of inhabitants (Zielona Góra and Opole regions) do not require separate paediatric oncology centres due to the low number of newly diagnosed patients. Children from these two regions are treated in neighbouring regions, within 100 km distance.

POLISH SOCIETY OF PAEDIATRIC ONCOLOGY AND HAEMATOLOGY

The beginnings of paediatric oncology in Poland date to January 2nd, 1962 when the Department of Oncology was set up by Prof. Józef Bożek in the Institute of Mother and Child in Warsaw. The Polish Paediatric Leukaemia and Lymphoma Study Group (PPLLSG) was founded by prof. Jerzy Armata in 1974, and the Polish Paediatric Solid Tumours Study Group (PPSTG) in 1992 by Prof. Urszula Radwańska.

The Polish Society of Paediatric Oncology and Haematology (PSPOH) was established in 1999 by prof. Janina Bogusławska-Jaworska on the basis of the Polish Paediatric Leukaemia and Lymphoma Study Group and the Polish Paediatric Solid Tumours Study Group.

Prof. Jerzy Kowalczyk was elected to be the first president of the Polish Society of Paediatric Oncology and Haematology serving two terms, 1999–2003 and 2003–2007; Prof. Danuta Perek was the president for the next two terms, 2007–2011 and 2011–2016, followed by Prof. Tomasz Szczepański from 2016.

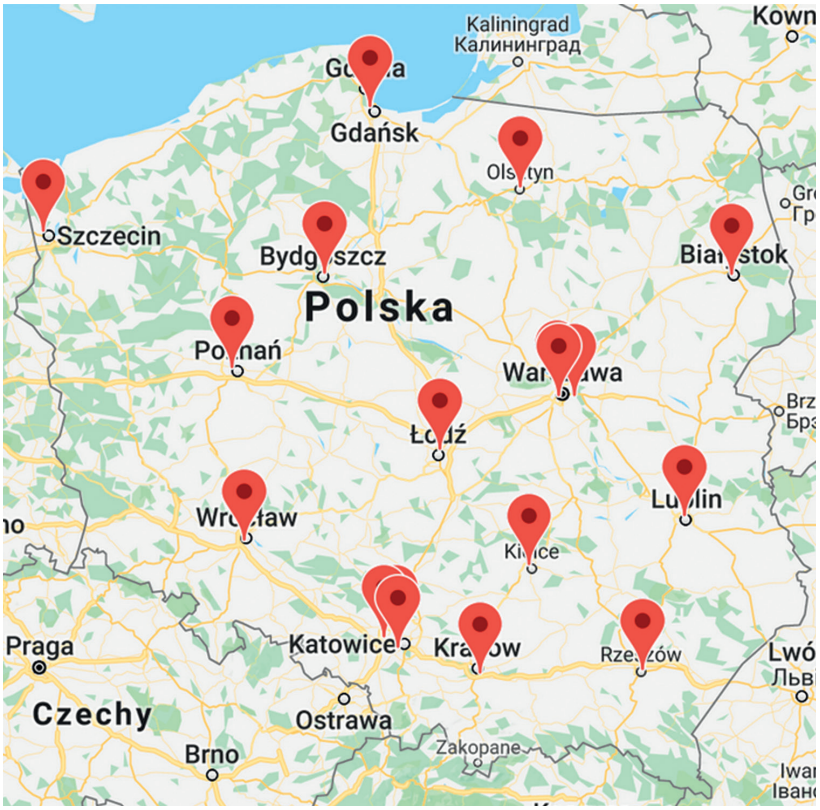

FIGURE 2. Oncological centres accredited by the Polish Society of Paediatric Oncology and Haematology

The First Congress of PSPOH was organised in 2001 in Bydgoszcz, followed by: Kraków (2003), Warsaw (2005), Białystok/Białowieża (2008), Szczecin/Międzyzdroje (2010), Łódź (2012), Olsztyn (2014), Zabrze/Katowice (2016), and Poznań (2018).

The PSPOH cooperates with a number of national (Polish Society of Paediatrics, Polish Society of Haematology and Blood Transfusion, Polish Society of Clinical and Experimental Immunology, Polish Society of Paediatric Surgery, Polish Transplantation Society, Polish Society of Radiation Oncology) and international (International Society of Paediatric Oncology; European Society for Paediatric Oncology, SIOPE; European Society for Blood and Marrow Transplantation; International BFM Study Group; European Intergroup for Childhood NHL; EWOG-MDS Study Group; Gesellschaft für Pädiatrische Onkologie und Hämatologie; European Network-Paediatric Hodgkin's Lymphoma Study Group; European Conference on Infections in Leukaemia – ECIL) scientific societies. Polish centres (Gdańsk, Lublin, Wrocław) are active members of the European Reference Network in Paediatric Oncology (ERNPaedCan).

Members of PSPOH are appointed for important international functions: Prof. Tomasz Szczepański was elected as the Main Representative of the National Paediatric Haemato-Oncology Societies (NaPHOS) within the SIOPE Clinical Research Council and SIOPE Board Member, and Prof. Jan Styczyński is the Chair of the Infectious Diseases Working Party (IDWP) of the European Society of Blood and Marrow Transplantation (EBMT); member of the Scientific Council and Board of EBMT, as vice-president of the ECIL.

NATIONAL CONSULTANT OF PAEDIATRIC ONCOLOGY AND HAEMATOLOGY

The function of the National Consultant of Paediatric Oncology and Haematology was established in 1991. Prof. Urszula Radwańska was appointed the first National Consultant in 1994–1995, and thus paediatric oncology was separated from clinical oncology, which was chaired by Prof. Maciej Krzakowski. From 1995 Prof. Jerzy Kowalczyk was the National Consultant for over 21 years, until 2017, followed by Prof. Jan Styczyński.

Current Regional Consultants in Paediatric Oncology and Haematology include: Prof. Tomasz Szczepański, Prof. Walentyna Balwierz, Prof. Elżbieta Drożyńska, Prof. Maryna Krawczuk-Rybak, Prof. Bernarda Kazanowska, Prof. Michał Matysiak, Prof. Jacek Wachowiak, Prof. Mariusz Wysocki, Prof. Jarosław Peregud-Pogorzelski, Dr hab. Beata Zalewska-Szewczyk, Dr hab. Ewa Gorczyńska, Dr Radosław Chaber, Dr Małgorzata Mitura-Lesiuk, Dr Wanda Badowska, and Dr Grażyna Karolczyk.

ONCOLOGICAL TREATMENT

Modern treatment for childhood cancer is based on multimodal therapy including multi-agent chemotherapy, radiotherapy, surgery, haematopoietic cell transplantation (HCT), and immunotherapy.

All children in Poland are treated according to international therapeutic protocols in cooperation with international centres, which run as academic clinical trials. With this approach, children with malignancy in Poland receive the same treatment as children in Western Europe.

In 2017, a total of 264 children received radiotherapy in the following malignancies: central nervous system (CNS) tumours (n = 95), neuroblastoma (n = 29), Ewing sarcoma (n = 26), acute lymphoblastic leukaemia (n = 24), Hodgkin lymphoma (n = 20), Wilms tumour (n = 15), rhabdomyosarcoma (n = 15), non-Hodgkin lymphoma (n = 6), osteosarcoma (n = 5), acute myeloblastic leukaemia (n = 3), and rare tumours (n = 13). Thirteen children received total body irradiation (TBI) before HCT.

Currently, HCTs are performed in six paediatric centres: Poznań (from 1989), Wrocław (from 1994), Lublin (from 1998), Kraków (from 2002), Bydgoszcz (from 2003), and Warsaw (from 2018).

PAEDIATRIC SURGICAL ONCOLOGY

Paediatric surgical oncology is one of the three main modalities of oncological therapy. The rarity of solid tumours in childhood implies a centralisation of this discipline in a few multidisciplinary, well equipped, and experienced centres. Such an effort has been undertaken on the both European (ERN) and national fields (PSPOH). Three to five paediatric surgical departments in Poland are considered to be the full- or nearly-full-profile, high-volume surgical oncology centres meeting the highest standards. Two of them are members of the ERNPeadCan EU system for paediatric onco-surgery; their responsibility includes expert advising and treating transferred difficult cases.

ADVANCES IN DIAGNOSTICS AND TREATMENT

HAEMATOLOGY

Since the early 1950s the history of Polish paediatric haematology began with prominent paediatricians; Prof. Maria Ochocka, Prof. Danuta Sońta-Jakimczyk, Prof. Wacława Celińska, Prof. Roma Rokicka-Milewska, Prof. Jerzy Armata, Prof. Urszula Radwańska, Prof. Janina Bogusławska-Jaworska, and many others. At present, haematology focuses on the diagnosis and treatment of all types of anaemias, coagulation disorders, and thrombocytopaenias. One of the greatest achievements is our participation in the European Diamond-Blackfan Anaemia Consortium directed by the Medical University of Warsaw, as well as the implementation of a program for the prevention of bleeding in children with haemophilia, a treatment program for chronic thrombocytopaenia, and chelation therapy. These programs were devised by the members of the Haematology Group of the PSPOH. A program to increasing awareness of haematological disorders through a series of lectures, conferences, and textbooks in the field of paediatric haematology was carried out.

HAEMOPHILIA: PROPHYLAXIS IN HAEMOPHILIA

A major advancement in the treatment of children with severe haemophilia came in the form of the prophylaxis program initiated in 2008 in Poland [2]. For several months all of the patients were included in a special national program with regular infusions of factor VIII or factor IX concentrates. Home deliveries of concentrates were provided. For the last 10 years the number of factor VIII IU/capita increased from 3.44 to 6.68, reflecting considerable achievement. In 2010 recombinant concentrates were introduced for children previously untreated with plasma-derived products. At present 40% of all children are currently treated with recombinants. All children who developed a high level of inhibitor started immune tolerance induction with the possibility of prophylaxis by regular injections of "bypassing" concentrates to prevent joint bleeds [3, 4]. Electronic diaries were implemented to register all concentrate injections during the prophylaxis program in 2018.

MOLECULAR TESTING IN PAEDIATRIC HAEMATOLOGY AND ONCOLOGY

Molecular testing has emerged as a routine approach that facilitates current treatment strategies. In 2016, a central genetic diagnostic laboratory for the whole Poland, called the Oncolab, was established in Łódź. Supported by the foundation of the Great Orchestra of Christmas Charity, this laboratory serves as a reference centre for genetic diagnosis of all known germline defects leading to haematological disorders, including haematological cancers, primary immunodeficiencies, and haemostatic disorders [5].

For instance, identification of germline defects predisposing to cancer, like Fanconi anaemia, Bloom syndrome, ataxia telangiectasia, Nijmegen syndrome (NBS), and many others, helps to adjust the therapy to the expected toxicity. Because NBS is common in the Slavic population (the frequency of c.657_661del5 founder mutation is 1/190), Poland became a leading country for the preparation of international recommendations for the management of these patients [6]. Moreover, access to modern technology like dense SNP arrays, exome sequencing, and deep RNA sequencing using next-generation sequencing (NGS) platforms has led to a risk stratification for leukaemia and lymphoma, which is currently enriched by the

molecular minimal residual disease (MRD) measurement and identification of molecular targets in leukemic cells. All of these molecular approaches are currently available in Oncolab. This is especially important for paediatric patients who have resistant of relapsed disease [7].

FLOW CYTOMETRY TESTING IN ACUTE LEUKAEMIA

Flow cytometry is a basic investigation for the characterisation of acute leukaemias. With the advent of multicolour cytometers, this diagnostics has become even more powerful. In 2006 the EuroFlow consortium "Flow cytometry for fast and sensitive diagnosis and follow-up of haematological malignancies" was established thanks to the European Community Framework 6 Program. The consortium has developed diagnostic algorithms, eight-colour antibody panels, uniform instrument settings, as well as specialised software for standardised multidimensional flow cytometric immunophenotyping of normal, reactive, and malignant leukocytes [8, 9]. The Department of Paediatric Haematology and Oncology in Zabrze of the Medical University of Silesia in Katowice was one of the founding centres of the EuroFlow consortium with a special contribution to acute leukaemia diagnostics [10–12]. The EuroFlow consortium has also established an inter-centre quality control program for the flow cytometric protocols [13]. Finally, the consortium has developed standardized eight-colour flow cytometry assays for highly sensitive MRD measurements in B-cell precursor ALL comparable to the gold standard of real-time quantitative polymerase chain reaction (RQ-PCR)-based MRD detection via antigen-receptor rearrangements [14, 15].

ACUTE LYMPHOBLASTIC LEUKAEMIA

Treatment of childhood acute lymphoblastic leukaemia (ALL) in Poland was generally based on BFM backbone protocols since 1980. Significant progress could be shown in two decades in terms of treatment results; event-free survival (EFS) at five years was 38% in 1982 and almost 70% in 2002 [16, 17]. This improved outcome can be attributed to the optimal risk-directed therapy that incorporates delayed intensification with vincristine, asparaginase, and dexamethasone, high-dose methotrexate, and early use of intrathecal therapy. In 2002 PPLLSG joined the ALL-IC-BFM-2002 trial, which was designed to be conducted in countries with inadequate skills and resources for PCR-based MRD monitoring. On the basis of the pioneering findings of the BFM group on measurement of early response to prednisone in peripheral blood on day 8 and the percentage of bone marrow blasts on day 15, all patients could be stratified in risk groups by accessible and cheap methods [18]. A total of 1782 patients were registered and treated according to that protocol between 2002 and 2011. The overall five-year EFS was 79% and overall survival (OS) was 86% for all 1782 eligible patients. The overall five-year EFS and five-year OS probabilities for the standard-risk (SR), intermediate-risk (IR), and high-risk (HR) group were 89% and 80%; 63% and 96%; and 87% and 70%, respectively. This successful trial was followed by the ALL IC BFM 2009 protocol started in 2012 and closed on 30.09.2018. Minimal residual disease measured by flow cytometry was added as an additional criterion for patient stratification. A total of 1201 children with ALL were treated according to ALL-IC-BFM-2009. The probability of overall five-year EFS was 90% and OS was 95% for the entire group of patients. The overall five-year EFS and five-year OS probabilities for the SR, IR, and HR groups is currently: 96% and 92%; 81% and 98%; and 97% and 87%, respectively. On 1.10.2018 a new protocol AIEOP-BFM-2017 was introduced in Poland with new stratification approach based on MRD measured both by flow and molecular methods and genetic evaluation of blasts.

INFANT ACUTE LYMPHOBLASTIC LEUKAEMIA

Infant ALL is a very aggressive disease with unique biology characterised by the presence of MLL gene rearrangements and generally inferior outcome [19]. Since December 1999 ALL patients in Poland are treated according to international INTERFANT protocols. The results of the INTERFANT'99 program has shown significant albeit not fully satisfactory improvement in treatment outcome. Overall four-year EFS and survival for all patients were 47% and 55.3%, respectively [20]. However, the majority of participant groups, including PPLLSG, observed better outcomes with INTERFANT'99 compared with historical controls both in terms of EFS as well as survival. The worst two-year EFS and OS concerned patients with congenital ALL and was approximately 20% [21]. Similar results were obtained for relapsed infant ALL (three-year OS after relapse of 24.9%) [22]. The study confirmed the role of HCT as a valuable treatment option for a subgroup of infant MLL-rearranged ALL carrying further poor prognostic factors [23].

ACUTE MYELOBLASTIC LEUKAEMIA

Before 1983 only about 10% children with acute myeloblastic leukaemia (AML) could be cured. Therapies based on AML-BFM protocols have led to a gradual increase in the five-year EFS from about 10% before 1983 to 52% after 2004 [24]. Since 2005 central verification of cell morphology, immunophenotyping, and cytogenetic results have been available. Since 2006 molecular studies have been gradually extended. The progress was achieved by intensification of the treatment, more accurate stratification to risk groups, development of refined supportive care, and reduction of the number of toxic deaths [25]. Unfortunately, the rate of relapses is still high. Therefore,

courtesy of Prof. Dirk Reinhardt, in 2015 a new treatment protocol (AML-BFM 2012 Registry) with stratification to the risk groups based on cytogenetic and molecular genetics changes, as well as treatment responses, was introduced. Developed diagnostic panels are expanded using the latest molecular biology techniques such as nested-PCR, Sanger sequencing, and RT-qPCR to the currently implemented NGS analyses to adapt the available procedures to the requirements of the latest therapeutic protocols. Further progress in AML therapy seems to be possible due to cooperation between oncology centres within large international study groups.

CHRONIC MYELOID LEUKAEMIA

Chronic myeloid leukaemia (CML) constitutes 2–3% of all leukaemias in paediatric patients (up to 10 new cases yearly in Poland). The presence of BCR-ABL fusion is crucial for targeted molecular therapy with tyrosine kinase inhibitors (TKI), which replaced HCT as a standard first-line therapy. Imatinib remains a treatment of choice for children with CML (according to the guidelines of the PPLLSG). The five-year OS rate is 96%, and the five-year EFS remains 81% [26]. Despite the excellent results of imatinib therapy, HCT is the only method for obtaining a definite cure of CML. HCT should be considered in patients refractory to imatinib or in children diagnosed before puberty, due to growth impairment after TKI therapy.

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes and juvenile myelomonocytic leukaemia are diagnosed and studied within international projects, providing the best therapeutic strategies. After 2005, patient survival in Poland increased from 30% to 57%. Advances in molecular diagnostics help to identify rare diseases manifesting with bone marrow failure [27].

NON-HODGKIN LYMPHOMA

Non-Hodgkin lymphoma (NHL) is the fourth most common malignancy in children, comprising a heterogenous group of histological entities varying according to age at diagnosis. The prognosis for children diagnosed with NHL has significantly improved over the last two decades, with an OS rate now exceeding 80% [28]. This has resulted from the application of multiagent chemotherapy at doses adjusted to subtype and stage of NHL, as well as the introduction of targeted therapies (rituximab: anti-CD20 monoclonal antibody). Such progress could not have been achieved without international collaboration and better understanding of the molecular biology of paediatric NHL [29, 30]. Challenges that remain include defining molecular and prognostic markers to improve risk stratification and developing innovative therapies.

HODGKIN LYMPHOMA

In Poland multidrug chemotherapy combined with involved field radiotherapy (IF-RT) was introduced for all stages of Hodgkin lymphoma (HL) in 1969. Initially, almost all patients were treated with chemotherapy and IF-RT. The intensity of therapy was gradually adjusted to the risk-factor groups, and invasive methods of staging were gradually limited. At the same time, supportive care was improved. The use of combined-modality therapy resulted in the cure of about 90% of children [31, 32]. However, the intensive treatment increased the risk of late complications, especially second malignancies. Therefore, treatment regimens with limited use of IF-RT were introduced. Thanks to Prof. Dieter Körholz, from June 2009 the EuroNet-PHL Protocols for classical type of HL are used in Polish centres. Treatment response assessment with PET allows the rate of patients treated without radiotherapy to be increased from 7% to 50% [33]. The use of chemotherapy as a single treatment modality in selected groups of patients did not impair the treatment results and decreased the risk of life-threatening complications.

BRAIN TUMOURS

Central nervous system (CNS) tumours are the most common solid tumours of childhood and are the first cause of cancer-related death in children younger than 15 years of age. In Poland the introduction of unified diagnostic and multidisciplinary therapeutic management of CNS tumours in children in 1996 resulted in significant improvement of treatment results, which at present are the same as in other childhood cancer centres in the world. At present over 70% of children with CNS tumours are cured. Unfortunately, brain tumour survivors experience severe late effects attributed to the disease itself, surgery, irradiation of CNS, and long-term toxicity of chemotherapy. Recent advances in molecular genetics have allowed us to precisely identify the tumour type and risk group, and stratify treatment accordingly. Identification and better understanding of molecular mechanisms of tumour growth and behaviour may help to establish molecular targeted therapies [34–36].

NEUROBLASTOMA

In Poland 60–70 children aged 0–18 years are diagnosed with neuroblastoma (NBL) each year. Before 2001, at least four different NBL treatment protocols were used in Poland. Between 1991 and 2001 the five-year EFS rate in infants and older children with NBL was 92% and 39%, respectively. The five-year EFS rate in children above one year of age with stage 4 was 22%. To improve the results in the high-risk patients and to decrease the rate of therapy-related side effects, since 2001 European treatment

protocols have been introduced systematically in Poland. Since 2006 cytogenetic examination and molecular studies have been gradually extended. All patients have evaluated MYCN gene copy number status by interphase FISH technique. Each NBL tumour is screened for chromosomal alteration by comparative genomic hybridization array (performed also on formalin-fixed paraffin-embedded samples). Additionally, the two most common mutations in ALK gene sequence in NB cells are detectable by Sanger sequencing from fresh as well as fixed samples. Improvement of five-year EFS from 22% to 40% in stage 4 NBL was observed [37–39]. Since February 2015, children have been treated with anty-GD2 (dinutuximab) immunotherapy in Kraków according to the SIOPEN HR-NBL protocol. Immunotherapy resulted in a further increase in five-year EFS in HR-NBL from 40% to 60%. Many issues concerning NBL treatment remain unsolved in Poland.

NEPHROBLASTOMA

Nephroblastoma (Wilms' tumour) is the most common malignant tumour of kidney origin and is the second (after neuroblastoma) embryonic extracranial solid tumour in children. The incidence is estimated to be seven per 1,000,000 children under 16 years of age. In Poland, the preferred method of treatment is consistent with the recommendations of the Renal Tumour Study Group SIOP and coordinated within the PPSTG. The protocol SIOP-2001 was approved in January 2002. Our database currently includes over 650 children. The results of treatment of children in Poland are comparable with European results [40]. At present, we are preparing to introduce a new protocol, called "Umbrella".

SOFT TISSUE SARCOMA

Soft tissue sarcomas (STS) are a heterogeneous group of malignant diseases. The most common type of children's STS is rhabdomyosarcoma (RMS). The TNM staging system is used in clinical classification. The patients need multidisciplinary care, such as surgery, intense chemotherapy, radiotherapy, and reconstructive surgery. Due to unification of therapy in 17 cooperating centres (PPSTG) remarkable progress has been obtained in the treatment of this cancer. Enormous experience was gained thanks to multi-centred, international prospective researches (IRS, CWS, AIEOP). Currently 70% of patients can be cured [41–43]. In Poland the treatment is based on CWS strategy, starting with the CWS-91 protocol. The process of treatment depends on clinical and bio-molecular risk factors, such as: Ki-67 expression, morphometry, and the presence of gene expressions: PAX3/FKHR, PAX7/FKHR, SYT/SSX1, SYT/SSX2, and EWS/FLI1. Despite the progress achieved in all cancer types, effective therapeutic methods, and new molecular and biological markers are still being sought. Introducing targeted therapy (INFORM cooperation) combined with chemotherapy gives a chance to improve effectiveness of treatment and might be a basis to reduce chemotherapy doses, thus reducing complications related to therapy.

BONE TUMOURS

Primary bone tumours account for 7–8% of all malignant neoplasms in children and adolescents in Poland. The most common are Ewing sarcoma and osteosarcoma followed by chondrosarcoma and fibrosarcoma. Great progress has been made not only in the outcome of these neoplasms (in the case of localised disease the cure rate is about 70%) but also in the improvement in quality of life attributed to limb-sparing surgeries, which are supported by 3D techniques and the application of growing endoprosthesis [44, 45]. At present, in Poland such surgeries are also conducted in children even under one year of age. Not long ago, patients suffering from refractory or relapsed disease had no chance for cure. Today, with the introduction of new therapeutic protocols, high-dose therapy followed by haematopoietic stem cell rescue, and also by conducting more extensive surgeries along with new radiation techniques, has allowed an improvement in patient survival to 15–40%. Currently, targeted therapies are more often applied in the treatment of primary bone tumours, which not only extend the patients' OS but also improve their quality of life [46]. In the near future in Poland a non-commercial clinical trial for children with Ewing sarcoma, including this type of modern treatment, will open.

GERM CELL TUMOURS

Extracranial germ cell tumours (GCT) are a heterogeneous group of malignant tumours that arise from primordial germ cells. They account for 3–4% of all childhood malignancies and differ in biology, pathological type, and localisation. The treatment outcomes have been excellent since chemotherapy schedules containing cisplatin were introduced in the 1970s. Long-term EFS rates range between 73% and 90% [47]. Because of this the treatment protocols of GCT have been largely similar for decades. The main problems to resolve in contemporary oncology therefore are: new strategies to improve the results of resistant tumour treatment and to minimise the late toxicities of chemotherapy in patients who survive. New protocols are being discussed and proposed in international GCT groups that specialise in this field [48]. International studies on the biology of GCT are initiated based on tumour samples collected from many centres [49]. In 2017 the PPSTG became affiliated as an associate member with the largest consortium in GCT studies in the world – the Malignant Germ Cell International Collaborative (MaGIC). It is expected that the PPSTSG will take part in the therapy protocols that MaGIC is developing.

RETINOBLASTOMA

Retinoblastoma is the most common primary intraocular malignant tumour in children, and it accounts for 2.5–3% of all childhood malignancies. In Poland approximately 25–30 new cases of retinoblastoma are diagnosed each year. Treatment of this tumour includes systemic chemotherapy, focal techniques, and external beam irradiation, as well as enucleation in some cases. Retinoblastoma has survival rates of over 90%, which prompted the development of approaches to save eyes and visual function without jeopardising final outcomes. In the last decade intra-arterial chemotherapy has developed for intraocular retinoblastoma and is implemented by many centres in the world. This method has been adopted in The Children's Memorial Health Institute in Warsaw. Since 2015, 61 eyes of 50 patients with intraocular retinoblastoma were treated with intra-arterial chemotherapy. It allowed the preservation of 85% of the treated eye globes [50]. Our experience confirms that intra-arterial chemotherapy is safe and effective for treatment of patients with intraocular retinoblastoma, and it is available in Poland.

RARE TUMOURS

Very rare paediatric tumours (VRT) are cancers occurring in less than two cases per million children and not included in existing diagnostic-therapeutic protocols. Most of them belong to groups XI and XII of the International Childhood Cancer Classification (ICCC), comprising carcinomas, melanomas, carcinoids, neuroendocrine neoplasms, non-germinal gonadal tumours, and many others. Due to their rarity, the prognosis in patients with VRT is uncertain because the treatment is based on case reports or small series of patients. In Poland, paediatric VRTs are registered and consulted by the Polish Paediatric Rare Tumour Study Group, acting since 2002 under the auspices of the Polish Society of Oncology and Haematology. To optimise VRT therapy, Poland, Italy, Germany, France, and the United Kingdom in 2008 started cooperation by setting up the European Cooperative Study for Paediatric Rare Tumours (EXPeRT) [51–53]. Numerous analyses form the basis for the creation of diagnostic and therapeutic recommendations for particular types of VRT in children.

HAEMATOPOIETIC CELL TRANSPLANTATION

In Poland, between 1989–2017, the number of paediatric haematopoietic stem cell transplant (HCT) centres expanded from one in 1989 to six in 2017, the total number of transplant beds increased from one to 45, and the annual number and rate of transplants increased from one per year (0.8/10 million) to 196 per year (268/10 million) [54]. During the analysed time period 2702 HCTs were performed, including 1860 (68.8%) allogeneic (allo-HCT) with 142 in 2017 and 842 (31.2%) autologous (auto-HCT) with 54 in 2017. Among 1860 allo-HCTs, 74.2% were performed for malignancy and 25.8% for non-malignant disorders. Among 842 auto-HCTs, 30.5% were done for haematological malignancies, while the remaining 69.5% were for solid tumours. Thus, it can be stated that in Poland the infrastructure indispensable to perform HCT in every child with indication for HCT was created during the last 30 years, and HCT became an important part of paediatric treatment, especially in paediatric oncology, haematology, and in primary immunodeficiencies.

SUPPORTIVE THERAPY

INFECTIOUS COMPLICATIONS

Infections are the major cause of morbidity and mortality in patients with cancer or undergoing HCT. In the study of the PSPOH, the cumulative incidence of bacterial, fungal, and viral infections in oncological patients was 26.3%, 7.9%, and 3.5%, respectively, in Polish centres, while the cumulative risk of infection in HCT patients was respectively 1.4-fold; 3.5-fold, and 15.7-fold higher [55, 56]. Recent results of survival from infection reached 94% in fungal disease – which is a world-class achievement for our Society – and over 96% survival in multi-resistant-bacterial and viral infections. From 2014, a national program of antifungal prophylaxis was implemented in a selected group of children with malignancy and/or undergoing HCT.

NUTRITION

Nutritional status plays a significant role in the therapeutic process in children with neoplastic conditions. Abnormal body composition, especially sarcopaenia observed both at diagnosis and during treatment, is an important factor worsening the effects of therapy in this group of patients. In 2016, on the initiative of PSPOH, a working group was established to develop nutritional recommendations for children with neoplastic diseases. In cooperation with the Polish Society for Clinical Nutrition of Children, nutritional workshops addressed to physicians and parents are carried out in Polish oncological centres. These workshops are designed to present the modern principles of nutrition in patients with malignancies.

PSYCHOSOCIAL SUPPORT

During cancer treatment it is recommended not only to monitor somatic functioning of the patient but also to give well-planned bio-psychosocial support [57]. As a part of psychological care, the support program in-

cludes: 1) providing parents and children with cancer with comprehensive information on the diagnosis and treatment; 2) each child with cancer should be offered psychological support; 3) planned psychological care includes diagnostic and therapeutic relations with the child and adolescents with cancer according to their developmental and individual needs; and 4) monitoring the level of adaptation to the treatment across the treatment course and at critical moments. The unified model of disclosure of cancer diagnosis was elaborated. Adaptation of the PedsQL™ Cancer Module (assesses quality of life) and PAT 2.0 (psychosocial adaptation tool) was undertaken [58, 59]. Polish experience in the introduction of the planned bio-psychosocial support was noticed and used in guidelines entitled "European Standards of Care for Children with Cancer".

LATE EFFECTS

In recent decades a considerable improvement in the treatment of childhood cancer was achieved, and more than 80% of children become long-term survivors; many of them present treatment-related adverse health complications. In the Polish cohort (> 2000 registered subjects) of childhood cancer survivors, we found normal function of all organs in 11.75% of survivors, whereas in 88.25% of cases one or more symptom or complaint suggesting organ dysfunction was observed; circulatory problems were the most frequent (31.7%); > 20% of survivors presented complaints or abnormal function of urinary tract, skin, dental, or skeletal/muscular problems or had difficulty with chewing. Obesity or short stature alone was observed in 21.4%, and a variety of endocrine problems (short stature, obesity, thyroid dysfunction, and gonad toxicity) were present in 15% of females and 21% of males. Dysfunction of gonads as the only problem occurred in 9.6% of girls and 13.4% of boys [60].

DISCLOSURE

The authors declare no conflict of interest.

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